

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)



22 DEC 2004

Applicant's or agent's file reference 4 -32564AUSN		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/07002	International filing date (day/month/year) 01.07.2003	Priority date (day/month/year) 02.07.2002	
International Patent Classification (IPC) or both national classification and IPC A61K31/135			
Applicant NOVARTIS AG			

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 5 sheets, including this cover sheet.
 - ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

- This report contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 19.12.2003	Date of completion of this report 06.10.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Beranová, P Telephone No. +49 30 25901-333 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/07002

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-11 as originally filed

Claims, Numbers

1-3 received on 07.04.2004 with letter of 02.04.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☒ the claims, Nos.: 4-10
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/07002**

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	-
	No: Claims	1-3
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-3
Industrial applicability (IA)	Yes: Claims	1-3
	No: Claims	-

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

5.1 Reference is made to the following document:

D1: WO 99 20261 A (PONIKAU JENS) 29 April 1999 (1999-04-29)

D6: HURLIMANN A ET AL: 'Asthma, rhinitis and dermatitis triggered by fungal infection: Therapeutic effects of terbinafine.' DERMATOLOGY (BASEL), vol. 202, no. 4, 2001, pages 330-332, XP008021353 ISSN: 1018-8665

5.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 and 3 is not new in the sense of Article 33(2) PCT.

The document **D1** discloses the use of anti-fungal agents (such as **terbinafine**) for the treatment of chronic fungal **rhinosinusitis** by application of the administered agent to the nasal-paranasal cavity (claims 1, 6 and 17).

The present claims 1 and 3 relate to the use of the same compound (terbinafine) for the same purpose (chronic rhinosinusitis), wherein they encompass any administration route, i.e. the administration route in these claims is neither specified nor restricted to a specific administration route.

It is therefore considered that D1 is relevant for novelty of the subject-matter of claims 1 and 3.

D6 reports cases of two patients suffering from tinea unguium, dermatitis and rhinoconjunctivitis (page 330, middle column, 2nd paragraph). In the Discussion (page 331, middle column), the authors conclude that antifungal therapy using (oral) terbinafine (250 mg/daily) is not only effective in the treatment of tinea unguium but also has beneficial therapeutic effects in cases of allergy symptoms such as rhinoconjunctivitis.

The only distinguishing feature of the present application over D6 is the **dosage regimen**. Thus, all that has been discovered is that an optimal amount of terbinafine is particularly effective in the treatment of chronic rhinosinusitis (description page 3, 1st paragraph). However, it is submitted that this newly discovered dosage regimen cannot in itself confer novelty on a known therapeutic application.

Furthermore, in the last paragraph of the Discussion, the authors clearly suggest that "the standard dose of terbinafine may be insufficient to completely eliminate the allergic symptoms", pointing to the use of an increased dose of terbinafine.

It is therefore considered that the subject-matter of claims 1 - 3 lacks novelty (Article 33(2) PCT).

5.3 Should the applicant overcome the above raised objections of lack of novelty, an inventive step has to be demonstrated over D1 and D6, as the present claimed subject-matter, as far as novel, appears to be obvious over said documents (Article 33(3) PCT), i.e. it is necessary to demonstrate any new and surprising technical advantage related to the oral administration of 625 or 725 mg terbinafine when treating chronic rhinosinusitis (compared to the mucoadministration reported in D1 and to the dosage described in D6).

5.4 As set out in Article 6 PCT, claims shall be clear. Therefore, the meaning of the terms of a claim should be clear for the person skilled in the art from the wording of the claim **alone** (see the Guidelines C-III, points 4.1 and 4.2). It is submitted that this requirement is not met in the case of claim 3 with regard to the expression "duration effective to reduce the symptoms of, or eliminate chronic rhinosinusitis".

Enclosure

-12-

EPO-BERLIN

07-04-2004

Claims

1. Use of terbinafine in free base or acid addition salt form in the manufacture of a medicament for the treatment of chronic rhinosinusitis comprising ~~from more than 500 mg to about 800 mg, preferably from about 600 mg to about 800 mg, especially about 625 mg~~ or 725 mg terbinafine base equivalent as hydrochloride, or a molar equivalent in other acid addition salt or free base form.
2. Use according to claim 1 in the manufacture of a medicament for the treatment of chronic rhinosinusitis formulated as an oral dosage form into tablet, minitab, powder, granule, capsule, pellet or liquid oral dosage form.
3. A method of treating chronic rhinosinusitis in a mammal comprising orally administering a composition comprising ~~from more than 500 mg to about 800 mg, preferably from about 600 mg to about 800 mg, especially about 625 mg or 725 mg~~ terbinafine base equivalent as hydrochloride per day, or a molar equivalent in other acid addition salt or free base form, for a duration effective to reduce the symptoms of, or eliminate chronic rhinosinusitis,
4. ~~The method of claim 3 wherein the mammal is human.~~
5. The method of claim 3 wherein the duration effective to reduce or eliminate chronic rhinosinusitis comprises 6 weeks.
6. The method of claim 3 wherein the composition is formulated into tablet, minitab, powder, granule, capsule, pellet or liquid oral dosage form.
7. The method of claim 6 wherein the composition is in tablet or minitab form.
8. The method of claim 7 wherein the tablet form comprises one tablet of about 625 mg or 725 mg terbinafine base equivalent as hydrochloride, or a molar equivalent in other acid addition salt or free base form, or comprises two or more tablets wherein the total, combined amount of terbinafine is about 625 mg or 725 mg terbinafine base equivalent as hydrochloride, or a molar equivalent in other acid addition salt or free base form.
9. ~~The method of claim 3, wherein the chronic rhinosinusitis has a fungal etiology.~~
3. 10. A pack containing a plurality of terbinafine medicaments as defined in claim 1 or ~~compositions as defined in claim 3~~ arranged to be dispensed in the method of ²any one of claims 3 to 9, where convenient together with instructions for use, such as a calendar pack.

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